

In the Claims:

Please cancel claim 1 without prejudice.

Please add the following new claims:

- 43. A yeast cell having a pheromone system, which cell comprises
  - (a) a first heterologous gene encoding a heterologous surrogate of a yeast pheromone receptor, said surrogate performing in the pheromone system of the yeast cell a function naturally performed by said yeast pheromone receptor, and
  - (b) a second heterologous gene encoding a heterologous peptide, wherein said heterologous peptide modulates the interaction of said surrogate with said pheromone system in the yeast cell, and said modulation is a selectable or screenable event.
- 44. The yeast cell of claim 43 in which the peptide is an agonist for the surrogate receptor.
- 45. The yeast cell of claim 43 in which the peptide is an antagonist for the surrogate receptor.
- 46. The yeast cell of claim 43, which further comprises a G protein, said G protein comprising a G $\alpha$  subunit, wherein said G $\alpha$  subunit is chimeric.
- 47. The yeast cell of claim 46 wherein the amino terminal portion of the G $\alpha$  subunit is substantially homologous with the G $\alpha$  subunit of a yeast G protein and the remainder is substantially homologous with the corresponding portion of a G $\alpha$  subunit of a heterologous G protein.

48. The yeast cell of claim 43 wherein the endogenous pheromone system protein is not produced in functional form.
49. The yeast cell of claim 43 wherein the heterologous peptide is secreted by the cell into the periplasmic space, from which it interacts with said surrogate.
50. The yeast cell of claim 49, wherein the heterologous peptide is expressed in the form of a precursor peptide comprising a cleavable leader peptide and a mature peptide, which leader peptide directs secretion of said heterologous peptide.
51. The yeast cell of claim 50 wherein the leader peptide corresponds to a leader peptide of the *Saccharomyces cerevisiae*  $\alpha$  factor or  $\alpha$ -factor.
52. The yeast cell of claim 43 in which a wild-type pheromone of the yeast pheromone system is not secreted.
53. The yeast cell of claim 49 wherein the heterologous peptide is also expressed in a nonsecretory form.
54. The yeast cell of claim 43, wherein the cell is a mutant strain having a pheromone signal pathway that is desensitized at slower rate relative to the wild type strain under the same conditions of continuous stimulation of the pheromone signal pathway.
55. The yeast cell of claim 54 in which the endogenous *SST2* gene is not functionally expressed.
56. The yeast cell of claim 43, in which the endogenous *FAR1* gene is not functionally expressed.
57. The yeast cell of claim 43, further comprising a selectable marker that is activated by the pheromone signal pathway.

58. The yeast cell of claim 57, said selectable marker comprising a pheromone-responsive promoter which is substantially homologous with an endogenous pheromone-responsive promoter, operably linked to a foreign selectable gene.
59. The yeast cell of claim 58 wherein the selectable gene is an IGP dehydratase gene.
60. The yeast cell of claim 58 wherein the homologous wild-type promoter is the *FUS1* promoter.
61. The yeast cell of claim 43 wherein the cells belong to the species *Saccharomyces cerevisiae*.
62. A yeast culture comprising a plurality of yeast cells according to claim 43, said yeast cells collectively expressing a peptide library.
63. A method of assaying a peptide for modulation of the activity of a non-yeast surrogate for a pheromone system protein which comprises providing yeast cells according to claim 43, which cells functionally express said heterologous surrogate and said heterologous peptide, and determining by detecting a change in said selectable or screenable event whether the pheromone signal pathway is activated or inhibited by the interaction of said surrogate and said peptide.
64. The method of claim 63 in which the cells comprise a pheromone-responsive selectable marker, and cells are selected for expression of a peptide having the desired activating or inhibiting effect.
65. The method of claim 63 in which the cells comprise a pheromone-responsive screenable marker, and cells are screened for expression of a peptide having the desired activating or inhibiting effect.
66. A method of assaying a peptide library for activity of a non-yeast pheromone system protein surrogate which comprises providing a yeast culture according to claim 62, whose cells each functionally express said surrogate and a peptide of said library, said culture collectively expressing the entire peptide library, and determining whether the

pheromone signal pathway is activated or inhibited by said peptides in each of the cells of said culture.

67. The yeast cell of claim 43 wherein said surrogate is the C5a receptor.
68. The method of claim 64 in which the surrogate is human Mdr1, the cells grow on histidine-free media only if the surrogate transports  $\alpha$ -factor, the cells are galactose-sensitive only if the surrogate transports  $\alpha$ -factor, and endogenous pleiotropic drug resistance genes have been inactivated.
69. A mixture of recombinant yeast cells, each cell of which comprises:
  - (i) a pheromone system generating a detectable signal;
  - (ii) an expressible gene construct encoding a heterologous surrogate of a yeast pheromone receptor, said surrogate performing in the pheromone system of the yeast cell a function naturally performed by said yeast pheromone receptor; and
  - (iii) an expressible gene construct encoding a heterologous peptide, wherein collectively the mixture of cells express a library of said heterologous peptides, and modulation of the pheromone system by the heterologous peptide provides the detectable signal.
70. The recombinant cells of claim 69, wherein the yeast pheromone receptor is inactivated.
71. The recombinant cells of claim 69, wherein each cell further comprises a marker gene construct containing a marker gene in operative linkage with one or more transcriptional regulatory elements responsive to the pheromone system, expression of the marker gene providing the detectable signal.

72. The recombinant cells of claim 71, wherein the marker gene that gives rise to a detectable signal selected from the group consisting of:  $\beta$  galactosidase, alkaline phosphatase, horseradish peroxidase, exoglucanase, luciferase, and chloramphenicol acetyl transferase.

73. The recombinant cells of claim 71, wherein the marker gene that gives rise to a detectable signal is a HIS 3 gene.

74. The recombinant cells of claim 69, wherein the population of heterologous peptides includes at least  $10^3$  different peptide sequences.

75. The recombinant cells of claim 69, wherein the population of heterologous peptides includes at least  $10^7$  different peptide sequences.

76. The recombinant cells of claim 69, wherein the yeast cell is a *Saccharomyces* cell.

77. A mixture of recombinant yeast cells, each cell of which comprises:  
(i) a pheromone system generating a detectable signal;  
(ii) an expressible gene construct encoding a heterologous surrogate of a yeast pheromone receptor, said surrogate performing in the pheromone system of the yeast cell a function naturally performed by said yeast pheromone receptor; and  
(iii) an expressible gene construct encoding a heterologous peptide, said heterologous peptide including a signal sequence for secretion into the periplasmic space, wherein collectively the mixture of cells express a library of said heterologous peptides, and modulation of the pheromone system by the heterologous peptide provides the detectable signal.

78. The recombinant cells of claim 77, wherein the yeast pheromone receptor is inactivated.

79. The recombinant cells of claim 77, wherein each cell further comprises a marker gene construct containing a marker gene in operative linkage with one or more transcriptional regulatory elements responsive to the pheromone system, expression of the marker gene providing the detectable signal.

80. The recombinant cells of claim 79, wherein the marker gene encodes a gene product that gives rise to a detectable signal selected from the group consisting of:  $\beta$  galactosidase, alkaline phosphatase, horseradish peroxidase, exo glucanase, luciferase, and chloramphenicol acetyl transferase.

81. The recombinant cells of claim 79, wherein the marker gene that gives rise to a detectable signal is a *HIS 3* gene.

82. The recombinant cells of claim 77, wherein the population of heterologous peptides includes at least  $10^3$  different peptide sequences.

83. The recombinant cells of claim 77, wherein the population of heterologous peptides includes at least  $10^7$  different peptide sequences.

84. The recombinant cells of claim 77, wherein the yeast cell is a *Saccharomyces* cell.

85. A method for identifying potential effectors of a yeast pheromone surrogate, comprising:

- (i) providing a mixture of recombinant yeast cells, each cell of which comprises
  - (a) a pheromone system generating a detectable signal;
  - (b) an expressible gene construct encoding a heterologous surrogate of a yeast pheromone receptor, said surrogate performing in the pheromone system of the yeast cell a function naturally performed by said yeast pheromone receptor; and
  - (c) an expressible gene construct encoding a heterologous peptide, wherein collectively the mixture of cells express a library of said heterologous peptides, and modulation of the pheromone system by the heterologous peptide provides the detectable signal; and
- (ii) isolating cells from the mixture which exhibit the detection signal.

86. The method of claim 85, wherein the yeast pheromone receptor is inactivated.

87. The method of claim 85, wherein said heterologous peptide includes a signal sequence for secretion into the periplasmic space.

88. The method of claim 85, wherein each cell of the mixture further comprises a marker gene construct containing a marker gene in operative linkage with one or more transcriptional regulatory elements responsive to the signal transduction activity of the cell surface receptor protein, and wherein expression of the marker gene provides the detection signal.
89. The method of claim 88, wherein the marker gene encodes a gene product that gives rise to a detection signal selected from the group consisting of:  $\beta$  galactosidase, alkaline phosphatase, horseradish peroxidase, exo glucanase, luciferase, and chloramphenicol acetyl transferase.
90. The method of claim 88, wherein the marker gene that gives rise to a detectable signal is a *HIS 3* gene.
91. The method of claim 85, wherein the population of heterologous peptides includes at least  $10^3$  different peptide sequences.
92. The method of claim 85, wherein the population of heterologous peptides includes at least  $10^7$  different peptide sequences.
93. The method of claim 85, wherein the yeast cell is a *Saccharomyces* cell.
94. The yeast cell of claim 43, wherein the yeast cell lacks ras function in the presence of cAMP.
95. The yeast cell of claim 94, wherein the yeast cell comprises a cam mutation.
96. The yeast cell of claim 43 wherein the yeast cell responds to a factor.
97. The yeast cell of claim 96, wherein the yeast cell expresses Ste 3p.
98. The yeast cell of claim 43, wherein the yeast cell responds to a factor and fails to grow on galactose.